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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

SODERQUIST, ARLEN

ART UNIT PAPER NUMBER

1743

DATE MAILED: 09/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/940,422

Applicant(s)

EDMEADES ET AL.

Examiner

Arlen Soderquist

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 July 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12, 14 and 15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12, 14 and 15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

2. Claim 12 is rejected under 35 U.S.C. 102(b,e) as being anticipated by Floyd (WO 97/00681 and US 5,492,510). In the published application and US Patent Floyd teaches a pharmaceutical composition containing lamotrigine. Column 2, lines 28-37 teach that due to undesirable instability of lamotrigine in aqueous media decomposition products such as 3-amino-5-keto-6-(2,3-dichlorophenyl)-1,2,4-triazine (the instantly claimed assayed compound) are known to form in injectable formulations. Tables 2 and 3 give results from assays of the compositions for stability. In Table 2, the first column under the related substances is for the compound 3-amino-s-keto-6-(2,3-dichlorophenyl)-1,2,4-triazine (footnote g), which is the instantly claimed 3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-(4H)-one. Footnote a of Table 3 teaches that the assay was a High Performance Liquid Chromatography (HPLC) procedure according to the Analytical Standard. In Table 3, the second column shows the concentration of the instantly claimed compound (see footnote b). On pages 8-10 of the publication and columns 5-6 of the patent a process of producing a pharmaceutical dosage and its stability testing is outlined. The process includes mixing the components together and drying them into a solid form (steps 1-9), stressing the dried product (step 10), reconstituting the dried product and assaying the product as outlined in tables 3-4 (steps 11-12). Instant claim 12 is anticipated based

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on the following two section of the instant specification. First page 5, lines 24-26 has the following sentence.

“Either lamotrigine itself (also referred to as drug substance) or a pharmaceutical dosage form comprising lamotrigine (also referred to as drug product) may be analysed for purity or stability to degradation.”

Second, page 21, lines 5-9 teach the following that is relevant to the claim scope and interpretation of the terms.

“ Throughout this specification and the appended claims it is to be understood that the words “comprise” and “include” and variations such as “comprises”, “comprising”, “includes”, “including” are to be interpreted inclusively, unless the context requires otherwise. That is, the use of these words may imply the inclusion of an element or elements not specifically recited.”

These two sections clearly show that “comprising lamotrigine” is not limited to the freebase form of the drug.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
 2. Ascertaining the differences between the prior art and the claims at issue.
 3. Resolving the level of ordinary skill in the pertinent art.
 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
4. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Floyd as applied to claim 12 above, and further in view of Papadoyannis. Floyd does not teach the use of standard solutions.

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In the paper Papadoyannis presents an efficient off-line solid-phase extraction (SPE) of lamotrigine (LTG) from human serum and urine prior to HPLC analysis. High extraction recoveries were achieved from C8 bond Elut cartridges (200mg/3ml), using acidic acetonitrile for the elution of LTG and the internal standard, 3,5-diamino-6-(2-methoxyphenyl)-1,2,4-triazine. Isocratic reversed-phase HPLC (RP-HPLC) analysis on octyl silica, using a Lichrosorb RP-8, 5 gm, 250 x 4.6 mm column and a mobile phase consisting of pH 5.6 0.05M acetate buffer-MeCN (72:28) was sensitive and rapid. The identification of LTG was performed by UV detection at 306nm. The method detected approximately 0.9 ng LTG on-column, using a 20- μ L loop, and linearity holds from ~ 0.044 to $7.8 \mu\text{g/mL}$ in standard solutions. These standard solutions were used to form a calibration chart for determining concentrations and also for checking the day-to-day precision and accuracy. In plasma and urine, the limits of detection are 1.1 and 1.2 ng, respectively, while linearity holds from ~ 0.087 to $3.49 \mu\text{g/mL}$. The proposed method was also used for the direct analysis of antiepileptic tablets.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use standard solutions in the Floyd method because as shown by Papadoyannis the standard solutions allow formation of calibration charts for determining concentrations and checking the day-to-day precision and accuracy.

5. Claims 12 and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dreassi in view of Floyd as explained above and Quaglia or DeAngelis. In the paper Dreassi teaches quantitative analysis of lamotrigine in plasma and tablets by planar chromatography and comparison with liquid chromatography and UV spectrophotometry. A method using planar chromatography (PC) was developed for determining lamotrigine (LTG) in human plasma and in tablets. LTG was extracted with MeCN in the presence of Na_2CO_3 . 3,5-Diamino-6-(2-methoxyphenyl)-1,2,4-triazine was used as an internal standard. The detection limit was $0.27 \mu\text{g/mL}$ plasma and the recovery from human plasma fortified with various concentrations of LTG was 91.3%. No interference from other common antiepileptic agents was found. The results obtained with the PC method were compared with those obtained by a method using liquid chromatography for analysis of plasma and tablets. On page 1278, Dreassi teaches the

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formation of calibration standards and the operating conditions including the method of quantification. Dreassi does not teach the quantification of any impurities.

In the paper Quaglia teaches the determination of chlorthalidone and its impurities in bulk and in dosage forms by high-performance thin-layer chromatographic densitometry. Chlorthalidone and its impurities were determined in bulk and pharmaceuticals by high-performance TLC-densitometry with dioxane-iso-ProH-25% NH₄OH-toluene-xylene (30:30:20:10:10) as the mobile phase. The relative standard deviation was 1.9% and the recovery of chlorthalidone and the impurities from artificial mixtures was 96.4-102.0%. Pages 436-437 teach the preparation of standards for Chlorthalidone and two of its impurities which were then used for calibration and calculation of the actual concentration. See figure 1 for an example chromatogram. The method was simple, accurate, reproducible, and selective.

In the paper DeAngelis describes a quantitative thin-layer chromatography (TLC) procedure for the analysis of the anticonvulsant cinromide (I, 3-bromo-N-ethylcinnamamide) [58473-74-8] and its 2 major metabolites, 3-bromocinnamamide [71539-43-0] and 3-bromocinnamic acid [32862-97-8], in plasma of a dog. These compounds were recovered from acidified plasma by extraction into benzene, with a recovery of 95%. All 3 compounds were quantitated directly on a TLC plate by UV absorbance densitometry at 270 nm. The linear range for the quantification of the compounds on a TLC plate was 10-1000 ng. The complete procedure is useful in the range 50-100 g/mL plasma, with a relative standard deviation of about 10%. The specificity of the method for the parent drug and each of its metabolites was confirmed by high-performance liquid chromatography. The method was used to determine the pharmacokinetics of cinromide and its 2 major plasma metabolites in dogs following a single oral dose of the drug. Pages 354-356 teach the preparation of standards of each of the compounds and the spotting of these standards and samples on to the TLC plates for quantification and verification of the samples.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the planar and liquid chromatography methods of Dreassi to determine stability/impurities in tablet or other formulations of lamotrigine as taught by Floyd using standards of lamotrigine and its known impurities as taught by Floyd because as taught by

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Quaglia or DeAngelis standard compositions of the expected or known components in the composition assist in verifying and quantifying the components of pharmaceutical formulations.

6. Applicant's arguments filed July 14, 2004 have been fully considered but they are not persuasive. Relative to the anticipation of claim 12 by Floyd, examiner points to the two sections of the instant specification reproduced above. From these sections it is abundantly clear that a formulation as found in the Floyd reference in which lamotrigine is in the form of a salt such as a mesylate is within the "comprising lamotrigine" language of claim 12. relative to the solid pharmaceutical language of the claim examiner points to the fact that the stress testing of Floyd is done on a lyophilized (solid) form of the drug. Since there is no limitation of the level of degradation of required, any level is within the claims. As these aspects of claim 12 are found in Floyd, they are not required to be taught by a secondary reference. Thus the Papadoyannis reference is there to show that in carrying out an analysis by HPLC as was taught in Floyd, one would have found it advantageous to use standard solutions to allow formation of calibration charts for determining concentrations and checking the day-to-day precision and accuracy. Relative to the combination based on the Dreassi reference, Floyd now teaches that the compound of the claims is known to be a degradation product of lamotrigine and is used to determine if and to what extent degradation has taken place. Floyd also teaches that this is desirable because of the undesirable aspects of lamotrigine degradation. Quaglia or DeAngelis support this combination by showing that standard compositions of the expected or known components in the composition assist in verifying and quantifying the components of pharmaceutical formulations.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose current telephone number is (571) 272-1265 as a result of the examiner moving to the new USPTO location. The examiner's schedule is variable between the hours of about 5:30 AM to about 5:00 PM on Monday through Thursday and alternate Fridays.

A general phone number for the organization to which this application is assigned is (571) 272-1700. The fax phone number to file official papers for this application or proceeding is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in cursive script, reading "Arlen Soderquist".

September 27, 2004

ARLEN SODERQUIST
PRIMARY EXAMINER